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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,459	04/01/2004	John T. Mulligan	340078.411	8500
500 7590 08/27/2007 SEED INTELLECTUAL PROPERTY LAW GROUP PLLC 701 FIFTH AVE SUITE 5400 SEATTLE, WA 98104			EXAMINER BERTAGNA, ANGELA MARIE	
			ART UNIT 1637	PAPER NUMBER
			MAIL DATE 08/27/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/816,459

Applicant(s)

MULLIGAN ET AL.

Examiner

Angela Bertagna

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 June 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-5 and 7-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-5 and 7-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 June 2007 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/19/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

1. Applicant's response filed June 19, 2007 is acknowledged. Claims 1, 3-5, and 7-15 are currently pending. In the response, claims 1, 7, 9, and 10 were amended, and claim 2 was cancelled.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/460,021, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The '021 application does not provide sufficient support for the method recited in claims 1, 3-5, and 7-15. Amended claim 1 recites separating heteroduplex nucleic acids that have interacted with a mismatch recognition protein from homoduplex nucleic acids that have not interacted with the mismatch recognition protein using a

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solid matrix that possesses a high affinity for protein and a low affinity for double-stranded nucleic acids. The '021 application recites separating heteroduplex DNA that has interacted with a mismatch recognition protein from homoduplex DNA that has not interacted with the mismatch recognition protein using DHPLC or gel shift analysis (see pages 9-10 and 14-16), but does not teach the use of a solid matrix having a high affinity for proteins and a low affinity for double-stranded oligonucleotides to effect this separation. Therefore, the '021 application does not provide sufficient support for the method of the instant claims 1, 3-5, and 7-15, and the filing date of Provisional Application No. 60/488,455 (July 18, 2003) has been used for prior art purposes.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on June 19, 2007 is acknowledged. A signed copy is enclosed.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

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5. Claims 1, 3-5, and 7-9 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Frey (US 2003/0134289 A1; newly cited). Regarding the rejection under 102(e), the Frey reference obtains benefit of Provisional Application 60/348,609, filed on January 14, 2002.

Regarding claim 1, Frey teaches a method of depleting in a sample of double-stranded oligonucleotides a population of double-stranded oligonucleotides containing mismatched bases thereby enriching in the sample a population of double-stranded oligonucleotides containing correctly matched bases, comprising:

(a) contacting the sample containing double-stranded oligonucleotides with a mismatch recognition protein in solution under conditions to permit the protein to interact with a double-stranded oligonucleotide containing at least one mismatched base (paragraphs 4, 8, and 53)

(b) separating the double-stranded oligonucleotide containing at least one mismatched base that has interacted with the mismatch recognition protein from double-stranded oligonucleotides that have not interacted with the mismatch recognition protein by contacting the sample of step (a) with a solid matrix that possesses high affinity for binding of protein and low affinity for binding double-stranded oligonucleotides (paragraphs 4, 8, and 53, where the immunoaffinity column binds proteins but not double-stranded nucleic acids)

(c) collecting double-stranded oligonucleotides that have not interacted with the mismatch recognition protein, thereby depleting the population of double-stranded oligonucleotides containing mismatched bases (paragraph 4).

Regarding claims 3 and 4, Frey teaches that the double-stranded oligonucleotides of the sample are chemically or enzymatically synthesized (paragraphs 61, 62, and 66).

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Regarding claim 5, Frey teaches that before step (a) in the method of claim 1, double-stranded oligonucleotides are denatured and reannealed under conditions to permit conversion of double-stranded oligonucleotides first to single-stranded oligonucleotides and then to double-stranded oligonucleotides (see paragraphs 61, 62, and 66, where Frey teaches the use of double-stranded nucleic acids generated by PCR amplification). These double-stranded nucleic acids have inherently been denatured and reannealed prior to step (a).

Regarding claims 7 and 8, Frey teaches that the double-stranded oligonucleotides are DNA comprising a portion of a gene (paragraphs 59 and 61).

Regarding claim 9, Frey teaches that the mismatch recognition protein is MutS (paragraph 7).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 10, 11, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frey (US 2003/0134289 A1; newly cited) in view of Lok et al. (US 2003/0143605 A1; newly cited). The Lok reference obtains benefit of Provisional Application 60/336,888, filed on December 3, 2001.

Frey teaches the method of claims 1, 3-5, and 7-9, as discussed above.

Frey teaches that biotin can be attached to a base pair mismatch or an insertion/deletion loop (paragraph 57), but does not teach that the biotin is attached to a nucleotide that is incorporated into the heteroduplex as required by claim 10.

Regarding claims 13 and 14, Frey teaches contacting the biotin-labeled heteroduplex with a support-immobilized avidin (paragraph 57).

Lok teaches methods for purifying perfectly matched double-stranded nucleic acids from a nucleic acid population comprising heteroduplex and homoduplex molecules (paragraph 16).

Regarding claims 10 and 13-15, the method of Lok comprises obtaining a sample containing heteroduplex and homoduplex polynucleotides (paragraphs 64-65), treating the sample with a mismatch recognition protein (paragraph 74), incorporating a biotin-labeled nucleotide into molecules that have interacted with the mismatch recognition enzyme (paragraph 74), contacting the sample with immobilized streptavidin to separate biotinylated heteroduplex nucleic acids from unlabeled homoduplex nucleic acids (paragraph 77).

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Regarding claim 11, Lok teaches that the mismatch recognition protein is CEL I endonuclease (paragraph 74). Lok teaches that, "CEL I is preferred due to its high specificity for insertions, deletions, and single-base pair substitution mismatches and its neutral pH optimal for activity, which is compatible with the activity of the polymerases employed for the nick translation reaction. Moreover, CEL I has the advantage in that its activity for making single-strand nicks at the site of nucleotide mismatch is stimulated in the presence of DNA polymerase (paragraph 56)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Lok to the method taught by Frey. An ordinary practitioner would have been motivated to further include a biotin incorporation step in order to more accurately distinguish nucleic acids that have interacted with the mismatch recognition protein from those that have not. Since the method taught by Lok separated heterduplex nucleic acids using a two-step procedure – binding of the mismatch recognition enzyme and nucleotide incorporation as a result of the binding (paragraph 74) – an ordinary practitioner would have recognized that this procedure would more accurately identify and label heteroduplex polynucleotides for removal from the population. An ordinary practitioner would also have been motivated to utilize CEL I as the mismatch recognition protein when performing the method of Frey, since Lok taught that this enzyme had a high specificity for insertions, deletions, and single-base substitutions in combination with an optimal activity at neutral pH (paragraph 56). As noted in MPEP 2144.06, it is prima facie obvious to substitute art-recognized equivalents known to be useful for the same purpose. Since Lok taught that CEL I was a mismatch recognition protein useful for binding and removing heteroduplex nucleic acids from a sample

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(paragraphs 56 and 74, for example), an ordinary practitioner would have been motivated to substitute this art-recognized equivalent for the mismatch recognition proteins taught by Frey. An ordinary practitioner would have had a reasonable expectation of success in applying the teachings of Lok to the method of Frey since both methods were directed to removal of heteroduplex DNA from PCR or oligonucleotide synthesis reactions. Thus, the methods of claims 10, 11, and 13-15 are prima facie obvious in view of the combined teachings of Frey and Lok.

8. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Frey (US 2003/0134289 A1; newly cited) in view of Lok et al. (US 2003/0143605 A1; newly cited) and further in view of Yanagihara et al. (Proceedings of the National Academy of Sciences, USA (2002) 99(17): 11317-11321; cited previously). The Yanagihara reference was first available online August 12, 2002.

The combined teachings of Frey and Lok result in the method of claim 10, as discussed above.

Neither Frey nor Lok teaches that the mismatch recognition enzyme is MuA transposase.

Yanagihara teaches a method of mapping genetic polymorphisms using MuA (see abstract). Yanagihara teaches that MuA transposase "exhibits a strong target site preference for all single-nucleotide mismatches (see abstract)." See also Figure 2A and page 11319 where Yanagihara states, "All eight types of mismatched base pairs were efficiently used as target (page 11319)." Yanagihara also teaches that the enzyme shows high sensitivity, as it is capable

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of cleaving single-nucleotide mismatches in the presence of 300,000-fold excess of non-mismatched sites (see abstract and Figure 3).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to utilize MuA transposase as the mismatch recognition protein in the method resulting from the combined teachings of Frey and Lok. Yanagihara taught that MuA transposase cleaved all single-nucleotide mismatches with a high degree of sensitivity (see abstract, Figure 2A and Figure 3 cited above). An ordinary practitioner would have been motivated by these teachings of Yanagihara to utilize MuA transposase in the method resulting from the combined teachings of Frey and Lok in order to obtain the ability to cleave and subsequently eliminate all mutated PCR products, thereby improving the purity of the isolated error-free products. An ordinary practitioner would have also been motivated to utilize MuA transposase, because Yanagihara taught that the enzyme was highly sensitive and was able to cleave mismatched targets even in the presence of a large excess of non-mismatched target (see abstract and Figure 3). An ordinary practitioner would have expected a reasonable level of success in using MuA transposase in the method resulting from the combined teachings of Frey and Lok, because Yanagihara used this enzyme with PCR products (see Figures 4 & 5). Thus, the method of claim 12 is prima facie obvious in view of the combined teachings of Frey, Lok, and Yanagihara.

Response to Arguments

9. Applicant's arguments, see page 8, filed June 19, 2007, with respect to the objections to the specification have been fully considered and are persuasive. Applicant's amendments overcome the objections, and therefore, they have been withdrawn.

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Applicant's arguments, see page 9, filed June 19, 2007, with respect to the rejection of claims 1-5 and 7-9 under 35 U.S.C. 102(b) as anticipated by Smith, have been fully considered and are persuasive. Smith does not teach all of the elements of claim 1 as amended, and therefore, the rejection has been withdrawn.

Applicant's arguments regarding the rejection of claims 10-15 under 35 U.S.C. 103(a) have been considered but are moot in view of the new grounds of rejection presented above.

Conclusion

No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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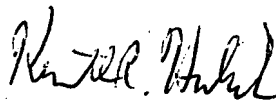
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Art Unit 1637 **AMB**
August 17, 2007

amb


KENNETH R. HORLICK, PH.D.
PRIMARY EXAMINER

8/21/07